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ROPES & GRAY LLP
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EXAMINER	
ANGELL, JON E	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/023,317	PLANK ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14 and 16-24* is/are pending in the application.

4a) Of the above claim(s) *22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,14,16-21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/17/2007.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Claims 1-11, 13, 14, 16-24 are currently pending.

2. Applicant's election without traverse of the species aliphatic polyester and implant in the reply filed on 11/17/2007 is acknowledged.

3. Claims 22 and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/17/2007.

4. Claims 1-11, 13, 14, 16-21 and 23 are examined herein.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 14, 16-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the claims are drawn to a composition comprising a carrier and a complex wherein the complex comprises a nucleic acid molecule and a charged copolymer wherein the charged copolymer is bound in the complex via ionic interactions and has the general formula as defined by formula I in claim 1. It is noted that the general formula as defined in claim 1 encompasses an enormous amount of different copolymer structures. The only disclosed use of the composition is for delivery of nucleic acid molecules into cells wherein the nucleic acid molecules have a biological affect when delivered into the cells. Therefore, the function of the composition is for delivery of nucleic acid molecules into cells. The genus of compositions encompassed by the claims is enormous because each composition could include a vast number of different copolymers and carriers wherein the structure of each carrier and of each copolymer differs. Since each composition encompassed by the claims is composed of a different combination of copolymer and carrier, each composition differs in its ability to facilitate delivery of a nucleic acid molecule into a cell and the claims may encompass compositions which do not facilitate delivery of nucleic acid molecules into cells. The

specification has disclosed PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12), which were shown in the indicated Examples as capable of delivering the nucleic acid molecule into a cell. However, the specification does not sufficiently describe the genus of compositions encompassed by the claims such that it would be readily apparent to one of skill in the art which compositions had the desired function (the ability to deliver the nucleic acid molecule into a cell) and which ones couldn't without performing additional experimentation. Accordingly, in the absence a sufficient disclosure, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the compositions having the intended function other than the ones specifically indicated above; therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at

1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the compositions comprising PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAP/cholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).)

Claims 1-11, 13, 14, 16-21 and 23 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12) and methods of using these composition and a method of transferring a nucleic acid into a cell using one of these specific compositions, does not reasonably provide enablement for the entire scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are drawn to a composition that is useful for transfer of nucleic acid molecules into cells wherein the composition comprises a complex comprising a nucleic acid molecule and a charged copolymer wherein the charge copolymer is bound in the complex via ionic interactions. The claims encompass a vast number of different compositions considering every possible copolymer encompassed by Formula I as defined in claim 1.

The relevant art teaches that there are a number of obstacles which must be overcome when using polymers for delivering nucleic acid molecules into cells. Specifically, Finsinger et al. (Gene Therapy, 2000; Vol. 7, pages 1183-1192) teaches,

> "In particular, it has been shown that nonviral gene vectors or their constituents interact strongly with blood components such as the complement system and other blood proteins. Such opsonization alters the physico-chemical characteristics of vectors, may interfere with vector targeting, and is of concern if vectors are to be applied in humans. Consequently, one major objective in nonviral vector development is to devise vectors which are inert in the in vivo environment during the delivery phase. Gene delivery in vivo comprises an extracellular and intracellular

delivery problem where solutions in one part must be compatible with the requirements of the other… In liposome and nanoparticle technology, poly(ethylene glycol) has been used to confer to these drug carriers the desired stability during the extracellular delivery phase. For the same purpose, PEG has been grafted covalently to preassembled polycation-DNA complexes. It was the aim of the work presented here to develop a new class of protective copolymers (PROCOPs) based on PEG which are assembled with nonviral gene vectors by electrostatic interaction." (See page 1183); and,

"Surface charge, particle size, and colloidal stability are interdependent physical characteristics of nonviral gene vectors with a strong impact on their biological properties including their efficiencies of gene delivery. The excess positive charge of lipoplexes and polyplexes, which is required for full DNA compaction and nuclease resistance, implies strong interactions with solutes (e.g. blood proteins, erythrocytes) and the extracellular matrix under in vivo conditions. The mostly undesired consequences can be unintentional vector targeting, complement activation, vector inactivation, and clearance by the reticulo-endothelial system." (See paragraph bridging pages 1186-1187).

Additionally, Choi et al (WO 9929839) teaches,

"On the other hand, non-viral gene delivery systems, such as cationic liposomes… have their drawbacks. Even though they seem to be safe for human clinical use, typical non-viral systems provide low transfection efficiencies, or cause precipitation of the nucleic acids… At present, LIPOFECTIN… protocol seems to be the most reliable in this category… but it bears the disadvantage of high toxicity…" (See page 2).

Choi et al. teach the design and use of a polymeric gene carrier comprising a grafted copolymer having a straight chain amphiphillic side polymers grafted to a polycationic main polymer (e.g., see abstract).

Therefore, although co-polymers were known in the art as being useful for gene delivery, there were still a number of obstacles that need to be overcome. Furthermore, the art only appears to teach the use of copolymers wherein the copolymers are grafted (i.e., covalently bound) in the complex. There does not appear to be any prior art where a complex comprising a nucleic acid molecule and a charged copolymer of Formula I,

wherein the charge copolymer is bound in the complex via ionic interactions (i.e. non-covalently bound).

The specification teaches that the following specific complexes were made and successfully used to deliver the nucleic acid molecule into cells: PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12).

Since the art indicates that there are a number of obstacles which must be overcome in order to be able to predictably deliver a nucleic acid into a cell using polymers, additional experimentation would be required to fully enable the entire scope of the instant claims. Considering the vast number of different compositions encompassed by the claims, an enormous amount of additional experimentation would be required. Furthermore, in addition to the obstacles recognized in the art, the fact that ionically bound copolymers have not been tested in the prior art, indicates that the additional experimentation required is not routine and it cannot be considered predictable that the entire scope of compositions encompassed by the claims would overcome all of the obstacles recognized in the art.

The level of the skill in the art is deemed to be high.

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope of the claims. Therefore, additional experimentation is

required before one of skill in the art could make and use the claimed invention. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

5. Applicant's arguments filed 6/22/2007 have been fully considered but they are not persuasive.

6. With respect to the written description rejections, Applicants argue that the disclosure satisfies the written description requirement because the specification and claims recite a specific chemical formula (I) for the copolymer of the claimed complex. Applicants also assert that all compounds of Formula I work and that Patent Laws do not require that every embodiment encompassed by the claims be an operable embodiment (citing MPEP 2164.08(b)).

7. In response, it appears that Applicants fail to recognize that the compounds of Formula I constitute an enormous genus of different molecules considering every molecule that meets the structural limitation of Formula I. Since each composition encompassed by the claims is composed of a different combination of copolymer and carrier, each composition differs in its ability to facilitate delivery of a nucleic acid molecule into a cell and the claims may encompass compositions which do not facilitate delivery of nucleic acid molecules into cells. The specification has disclosed the specific copolymer complexes of Examples 9-12 which are shown as capable of delivering the nucleic acid molecule into a cell. As such, the specification has only shown possession of these 5 specific copolymer complexes and rely on these specific molecules to

description of the entire genus. However, the genus encompasses molecules that are structurally related, may be functionally distinct. Furthermore, the specification does not indicate which molecules beyond those indicated (Examples 9-12) would have the desired function. Furthermore, it is respectfully pointed out that MPEP2164.08(b) indicates that although the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (Emphasis added). In the instant case, a skilled person could not determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. The expenditure of effort is more that is normally required considering the vast number of different molecules encompassed by claims. Therefore the disclosure does not meet the written description requirement for the entire genus of molecules encompassed by the claims.

With respect to the scope of enablement rejection, Applicants argue that the cited documents do not demonstrate that numerous obstacles exist for using polymeric compositions to deliver nucleic acids into cells. Applicants assert that Finsinger provides no evidence that there are many obstacles that must be overcome. Applicants contend that Finsinger is evidence that its complexes represent an efficient and viable means for introducing nucleic acid molecules into cells.

In response, it is respectfully pointed out that Finsinger teaches that opsonization may interfere with vector targeting; extracellular and intracellular delivery problems exist such that solutions in one part must be compatible with the requirements of the other; Surface charge, particle size, and colloidal stability can have a strong impact on the efficiency of delivery; excess positive charge, which is required for full DNA compaction and nuclease resistance, implies strong interactions with solutes (e.g. blood proteins, erythrocytes) and the extracellular matrix under in vivo conditions. Finsinger explicitly teaches, "The mostly undesired consequences can be unintentional vector targeting, complement activation, vector inactivation, and clearance by the reticulo-endothelial system." (See paragraph bridging pages 1186-1187). Therefore, Finsinger does teach a number of specific problems that must be overcome. Furthermore, although Finsinger indicates that copolymers obtained from YE5C and INF7 stabilize polyplexes at small size and-protect from complement activation and opsonization and that nonviral vectors can be protected with these copolymers and confer compatibility with the cellular steps of gene delivery, this appears to be Finsinger's solution to the problems. That is Finsinger teaches that copolymers obtained from YE5C and INF7 may overcome the art recognized problems. It is noted, however, that the instant claims do not indicated that the copolymers are obtained from YE5C and INF7. Therefore, the problems taught by Finsinger are applicable to the instantly claimed genus of copolymers, absent evidence to the contrary.

Applicants argue that Choi refers to gene delivery systems such as cationic liposomes and does not refer to copolymer complexes. Applicants contend that Choi

recites a copolymer complex for delivery of nucleic acids into cells that is safe and efficient.

In response, it is noted that it is NOT the Office's position that all copolymer complexes are not enabled. Rather, the art teaches that there are a number of significant obstacles that must be overcome for nucleic acid delivery into cells. In the instant case, the claims encompass a large genus of copolymer complexes for delivery of a nucleic acid, but the specification has only demonstrated a few of the copolymer complexes which overcome the art-recognized obstacles. However, this is not sufficient to enable all of the copolymer complexes of the entire genus of complexes encompassed by the claims. Furthermore, Choi does support the notion that there are obstacles that must be overcome for delivery of nucleic acid molecules into cells.

Applicants argue that the specification enables the full scope of the claimed invention. Applicants contend that the specification has taught how to make the copolymers of Formula I and have provided working examples that are illustrative examples that confirm that the claimed composition, in its full scope is enabled. Applicants cite MPEP 2164.02 as indicating

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.

Applicants assert that based on the teachings of the application and the level of skill in the art, no undue experimentation is required.

It is noted that MPEP2164.02 also indicates

> Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

In the instant case, based on the teachings of the prior art, adequate reasons have been advances to establish a person skilled in the art could not use the genus as a whole without undue experimentation. Especially in view of the enormous number of molecules that are encompassed by the claims.

8. The Declaration of Dr. Plank under 37 CFR 1.132 filed 6/22/2007 is insufficient to overcome the rejection of claims under 35 U.S.C. 112, first paragraph (scope of enablement) as set forth in the last Office for the following reasons. First, it is acknowledged that the Declaration states that two additional copolymer complexes which meet the structural limitations of Formula I can be used to deliver nucleic acid molecules into cells. Although this demonstrates that these two specific copolymers are enabled, the Declaration does not provide enablement for the entire scope of the claims. The evidence provided merely indicates that these two specific copolymers of the genus are enabled. The evidence does not provide enablement for all copolymers encompassed by the claims because the evidence presented does not demonstrate how to overcome the art-recognized obstacles for all of the other copolymers encompassed by the claims. It is noted that the instant application does not appear to disclose the specific copolymers used in the experiments of the Declaration, thus should applicants wish to amend the claims to include these specific embodiments with the indicated as being enabled, they should indicate where support for the copolymers can be found. Furthermore, considering the vast number of copolymers encompassed by the claims, an enormous amount of

additional experimentation would be required to enable the entire genus of molecules encompassed by the claims. The additional experimentation is beyond routine and is considered to be undue.

9. Therefore, Applicants arguments and the Declaration are not sufficient to overcome the rejection of claims under 35 USC 112, first paragraph.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635